1493

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#12
12/6/10

In re Application of

MEISEL et al.

Appln. No. 09/181,671 Group Art Unit: 1621

Filed: October 29, 1998 Examiner: DAVIS, B.

Title: NOVEL MODIFICATIONS OF 2-AMINO-4-(4-FLUOROBENZYLAMINO)-1-ETHOXYCARBONYLAMINOBENZENE, AND PROCESSES FOR THEIR PREPARATION

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November 28, 2000

BRIEF ON APPEAL

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Appellants submit herewith their Appeal brief in triplicate, pursuant to 37 C.F.R. §1.192.

(1) REAL PARTIES IN INTEREST

The real party in interest is ASTA Medica Aktiengesellschaft, by way of an Assignment executed by the inventors on February 17, 1998, February 18, 1998, February 25, 1999 and March 3, 1998, and recorded in the U.S. Patent and Trademark Office on October 29, 1998 at Reel 9562, Frame 0753.

(2) RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to the Appellants or the Appellants' legal representative, or the assignee, that will directly affect or will be directly affected by or have bearing on the Board's decision in this appeal.

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(3) STATUS OF CLAIMS

Claims 1-3 and 16 are pending. All pending claims have been finally rejected and are at issue in this Appeal. A copy of the pending claims is attached hereto as Appendix A to this Brief. Claims 1, 2, 3 and 16 are all independent claims.

(4) STATUS OF AMENDMENTS

The Examiner's Advisory Action mailed August 4, 2000 indicated that the Applicants' Declaration, filed July 21, 2000 together with Applicants' After Final Response was considered, and therefore is of record. No outstanding amendments to the claims exist, and thus the claims presented in Appendix A reflect the claims as amended August 26, 1999.

(5) SUMMARY OF THE INVENTION

In one embodiment, the claimed invention is a modification of the compound 2-amino-4-(4-fluorobenzylamino)-1 ethoxycarbonylamino benzene of formula I as characterized by X-ray diffractogram in which reflections not coinciding with the reflections of the other two modifications observed, *inter alia*, at 6.97°2θ (12.67 Å), 18.02°2θ (4.92 Å) and 19.94°2θ (4.45 Å).

In another embodiment, the claimed invention is a modification of the compound 2-amino-4-(4-fluorobenzylamino)-1 ethoxycarbonylamino benzene of formula I as characterized by X-ray diffractogram in which reflections not coinciding with the reflections of the other two modifications observed, *inter alia*, at 15.00°2θ (5.90 Å), 19.29°2θ (4.60 Å) and 19.58°2θ (4.53Å).

Still another embodiment of the claimed invention is a modification of the compound 2-amino-4-(4-fluorobenzylamino)-1 ethoxycarbonylamino benzene of formula I as characterized by X-ray diffractogram in which reflections not coinciding with the reflections of the other two modifications observed, *inter alia*, at 9.70°2θ (9.11 Å) and 21.74°θ (4.09 Å).

Yet another embodiment of the claimed invention are pharmaceuticals comprising the modification A, B, or C of compound I, and, if appropriate, excipients and/or auxiliaries.

(6) ISSUES

Whether claims 1, 2, 3 and 16 define an invention patentable over German Patent No. 4,200,259 in view of pages 700-702 of the Kirk-Othmer Encyclopedia of Chemical Technology, 4th ed., Vol. 7, 1993?

Claim 1 is directed to modification A of 2-amino-4-(4-fluorobenzylamino)-1 ethoxycarbonylamino benzene, which is the compound of formula I, having X-ray diffractogram parameters of 6.97°2θ (12.67 Å), 18.02°2θ (4.92 Å) and 19.94°2θ (4.45 Å).

Claim 2 is directed to modification B of compound I having X-ray diffractogram parameters of 15.00°2θ (5.90 Å), 19.29°2θ (4.60 Å) and 19.58°2θ (4.53Å).

Claim 3 is directed to modification C of compound I having X-ray diffractogram parameters of 9.70°2θ (9.11 Å) and 21.74°θ (4.09 Å).

Claim 16 is directed to pharmaceuticals comprising modifications A, B, or C of compound I and exipients and/or auxiliaries.

(7) GROUPING OF THE CLAIMS

The claims do not stand or fall together, pursuant to 37 C.F.R. §1.192(c)(7). The claims are separately patentable over German Patent No. 42 00 259 (hereinafter DE '259) in view of pages 700-702 of the *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed., Vol. 7, 1993 (hereinafter Kirk-Othmer, 1993).

(8) ARGUMENT

Appellants respectfully submit that the Examiner failed to present a *prima facie* case of obviousness under 35 U.S.C. §103(a). The Examiner has the initial burden of presenting a *prima facie* case of obviousness when making a Section 103(a)-based rejection. *In Re Rijckaert*, 28 U.S.P.Q2d 1955, 1956 (Fed. Cir. 1993). A *prima facie* case of obvious ness is established if the prior art suggested to one of ordinary skill in the art to modify the prior art in such a fashion as to produce the claimed invention, and that such a modification would reasonably have been expected to succeed. *In Re Dow Chemical*, 5. U.S.P.Q. 1529, 1531 (Fed. Cir. 1988).

The claimed invention is neither suggested nor disclosed by DE '259 in combination with Kirk-Othmer, 1993. The Examiner contends that crystalline modifications A, B, and C of formula I are inherent in the cited art. The Examiner asserts that because the compound of formula I is known, as per DE '259, crystalline polymorphisms of this compound are inherent. The Examiner relies on the teachings of Kirk-Othmer, 1993 to make these inherency arguments, stating that Kirk-Othmer, 1993 discloses "it is generally known in the chemical arts that many compounds crystallize in two or more distinct forms, morphologies and that these forms will have distinct properties with some forms, because those properties being [sic] more desirable/useful than others". *See* October 20, 1999 Office Action at page 5, paragraph 11. Consequently, the Examiner argues that crystalline forms of compound I are not patentably distinct over the combined teachings of DE '259 in combination with Kirk-Othmer, 1993. *See* October 20, 1999 Office Action at page 5, paragraph 12.

The Examiner suggested that Appellants submit a Declaration comparing the diffraction patterns of prior art crystals with those of the three claimed modifications of formula I. The Examiner stated that if the diffraction patterns are indeed different and distinct, then the instant claims would be allowable, provided that the prior art does not enable the preparation of the instantly claimed forms." *See* March 27, 2000 Office Action at page 2, paragraph 3.

Responsive to the Examiner's invitation, Appellants submitted a Declaration of inventor Wilfried Thiel, which showed a side-by-side comparison of the diffractograms of "Batch 9403001" (Figure 1) and "Batch 9403002 (Figure 2) of 2-amino-4-(4-fluorobenzylamino)-1 ethoxycarbonylamino benzene, prepared according to the methods of the cited art, and the three new crystalline forms of the invention, modifications A, B, and C. Figures 1 and 2 clearly show that the three claimed modifications A, B, and C are different from one another and are different from the heterogeneous preparations of the cited art, which are mixtures of different crystalline forms.

Mixtures of crystalline forms are a great problem for the pharmaceutical industry, as such mixtures confer undesirable properties on pharmaceutical preparations, making constant production of a uniform, highly active product difficult to achieve. *See* instant specification at page 1, line 31 through page 2, line 5. The claimed invention is directed to the first known pure homogeneous crystalline

modifications of 2-amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylamino benzene, each having a characteristic X-ray powder diffractogram. Each of claimed modifications A, B, and C have different physicochemical properties, and can be processed to yield pharmaceutical preparations meeting the demands of the pharmaceutical industry. *See* instant specification at page 6, lines 3-6. For example, modification A is stable below 80°C, even at elevated temperatures and humidities, and exhibits no change in crystalline structure upon contact with various solvents. *See* instant specification at page 6, lines 24-36. Modifications B and C are stable up to 142°C and 130°C, respectively, and can be used in galenic processes requiring the use of high temperatures. *See* instant specification at page 3, line 29 through page 4, line 11. Thus, the claimed invention overcomes a problem recognized in the pharmaceutical arts, providing for the first time specific modifications A, B, and C of the compound of formula I and pharmaceuticals comprising modifications A, B, and C.

In the case of crystal modifications, there is a very sharp "kind" criterion which is the crystal structure (including Bravais lattice, atom positions in the elemental cell, possible crystal forms, etc.) Furthermore, the structure can be identified by X-ray diffraction, as recited for presently claimed modifications A, B and C in the claims. The Examiner has stated that "the instant crystalline morphologies would have been obvious to one of ordinary skill in the art." (*See* paper no. 6, page 4, lines 8-9). Appellants respectfully disagree. Quartz was described for the first time by Agricola (1529), tridymite by Rath (1868), cristobalite by Rath (1887), coesite by Sosman (1954), stishovite by Chao, Fahey, Littler & Milton (1962), yet all of these forms are represented by the chemical structure SiO_2. The structure of the monoclinic form of the drug carbamazepine was solved in 1991 by Himes, but the trigonal form of carbamazepine was not described until 1987 by Lowes et al. Up until now, it has not been possible to answer the question of whether there are more SiO_2 or carbamazepine (or Retigabine) modifications. Attempts to calculate the possible crystal structures of a chemical compound have been successful only in a few special cases.

There may exist one or several modifications of one element or compound. However, there do not exist an endless number of modifications, because modifications correspond to arrangements of molecules with minimal free energy versus temperature and pressure. This results in ranges of stability for the different modifications.

DE '259 in combination with Kirk-Othmer, 1993 fails to teach the claimed invention. DE '259 discloses a 2-amino-4-(4-flurobenzylamino)-1-ethoxycarbonylaminobenzene of formula I in a mixture of products varying in crystal size and form. DE '259 does not disclose how to prepare the compound of formula I in homogeneous crystalline forms or which forms would be desirable for certain pharmaceutical preparations. Kirk-Othmer, 1993 fails to overcome the deficiencies of DE '259, as Kirk-Othmer, 1993 merely teaches that, in general, chemical compounds may crystallize into different forms. Kirk-Othmer, 1993 teaches that, for example, ammonium nitrate exhibits four changes in form between the temperatures of –18°C and 125°C. No suggestion or teaching is offered that would direct a skilled artisan to prepare the claimed modifications of the compound of formula I according to the claimed diffractogram parameters. Appellants note that it is improper to use the instant specification as an instruction book in an effort to reconstruct the prior art to arrive at the claimed invention. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561 (Fed. Cir. 1987).

At best, the combination of DE '259 and Kirk-Othmer, 1993 teaches that the compound of formula I might have polymorphisms that might be separable. Without teaching the specific parameters claimed or the process by which claimed modifications A, B, and C are to be isolated, the combination of DE '259 and Kirk-Othmer, 1993 invites experimentation to assess whether or not such modifications can be isolated. Whether or not a particular combination might be "obvious to try" is not a legitimate test of patentability. *In Re Geiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987).

In view of the foregoing reasons, Appellants respectfully submit that DE '259 in combination with Kirk-Othmer, 1993 does not establish a *prima facie* case of obviousness over the claimed invention.

Modification A of compound I as recited in claim 1 is separately patentable over DE '259 in combination with Kirk-Othmer, 1993, as these references fail to suggest, specifically or inherently, the claimed modification having the claimed X-ray diffractogram parameters of 6.97°2θ (12.67 Å), 18.02°2θ (4.92 Å) and 19.94°2θ (4.45 Å).

Modification B of compound I as recited in claim 2 is separately patentable over DE '259 in combination with Kirk-Othmer, 1993, as these references fail to suggest, specifically or inherently, the claimed modification having the claimed X-ray diffractogram parameters of 15.00°2θ (5.90 Å), 19.29°2θ (4.60 Å) and 19.58°2θ (4.53Å).

Modification C of compound I as recited in claim 3 is separately patentable over DE '259 in combination with Kirk-Othmer, 1993, as these references fail to suggest, specifically or inherently, the claimed modification having the claimed X-ray diffractogram parameters of 9.70°2θ (9.11 Å) and 21.74°θ (4.09 Å).

Pharmaceuticals comprising modifications A, B, or C of compound I as recited in claim 16 are separately patentable over DE '259 in combination with Kirk-Othmer, 1993, as these references fail to suggest, specifically or inherently, the claimed modifications having the claimed X-ray diffractogram parameters.

Appellants find no suggestion in DE '259 in combination with Kirk-Othmer, 1993 to isolate modifications A, B, or C of compound I, nor any teaching as to which X-ray diffractogram parameters would define these modifications. The Examiner asserts in the Advisory Action of August 8, 2000 that Modifications A, B and C are "inherent in the prior art" and that Kirk-Othmer, 1993 "provides the motivation to separate the three modifications." *See* Advisory Action at paragraph 6. Such facile logic fails to recognize the need to define Modifications A, B and C, as well as the conditions required for their separation. This information is taught in Appellant's specification, not the cited art.

The Examiner has, at best, rejected the claims based on a proverbial fishing expedition grounded in an "obvious to try" argument, not a *prima facie* case of obviousness. Appellants respectfully submit that claims 1-3 and 16 are not rendered obvious by DE '259 in combination with Kirk-Othmer, 1993, and that the Examiner's rejection should be reversed.

Respectfully submitted,

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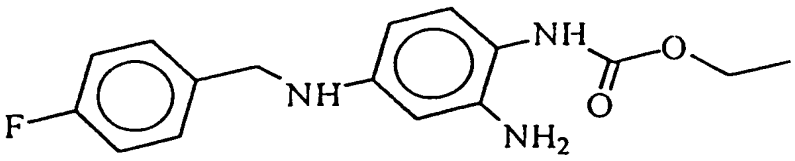
APPENDIX A

1. Modification A of the compound I



characterized by the X-ray diffractogram, reflections not coinciding with the reflections of the other two modifications being observed, *inter alia*, at 6.97°2θ (12.67 Å), 18.02°2θ (4.92 Å) and 19.94°2θ (4.45 Å).

2. Modification B of the compound I characterized by the X-ray diffractogram, reflections not coinciding with the reflections of the other two modifications being observed, *inter alia*, at 15.00°2θ (5.90 Å), 19.29°2θ (4.60 Å) and 19.58°2θ (4.53Å).

3. Modification C of the compound I characterized by the X-ray diffractogram, reflections not coinciding with the reflections of the other two modifications being observed, *inter alia*, at 9.70°2θ (9.11 Å) and 21.74°θ (4.09 Å).

16. Pharmaceuticals comprising the modification A, B or C of the compound I and, if appropriate, exipients and/or auxiliaries.